IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Gérard Grassy et al.

Serial No. 09/359,181

Filed: July 22, 1999

For: *Computer-Aided Method for the* Provision, Identification, and Description of Molecules Capable of Exhibiting a Desired Behavior, More Particularly in the Pharmaceutical Sector, and Molecules Obtained by Said Method

Examiner: Lori A. Clow

Group Art Unit: 1631

DECLARATION

I, Han van de Waterbeemd, hereby declare that:

1. I am a citizen of The Netherlands and reside at 13 Kerry Hill Way, Maidstone, Kent ME14 2GZ, UK.

2. I received a Ph.D. degree in 1980 from the University of Leiden, The Netherlands, after studying at the School of Pharmacy, today known as the Center for Bio-Pharmaceutical Sciences in the Department of Medicinal Chemistry, University of Leiden and submitting a thesis entitled "The relationship between partition coefficients and rate constants of drug partitioning and the application in QSAR".

3. From 1980 to 1988 I worked as a post-doctoral student and research assistant in the Department of Medicinal Chemistry, School of Pharmacy, University of Lausanne, Switzerland and performed studies looking at structure-activity relationships using chemometrics and molecular modelling techniques. From 1987 to 1996 I was a lecturer at the University of Bern, Switzerland and from 1995 to 1997 a lecturer at the Pharmaceutical Institute of the University of Basel, Switzerland.

4. In 1988 I joined Hoffmann-La Roche Ltd. in Basel, Switzerland, working from 1989 to 1997 as head of the Structure-Property Correlations Group in the Computational Chemistry Section of the Pharma Research New Technologies department.

5. In 1997 I joined Pfizer Central Research in Sandwich, UK as a manager in the department of Drug Metabolism and with responsibilities for drug discovery support. In 2002 I became head of Drug Metabolism Technologies in PDM (Pharmacokinetics, Dynamics and Metabolism) at Pfizer Global Research and Development in Sandwich, UK. Since 2003 I have been head of In Silico & Automation Technologies in PDM at Pfizer Global Research and Development, Sandwich, UK.

6. My research interests focus on physicochemical properties of biologically active compounds, bioavailability and drug transport processes, measurement and prediction of ADMET properties, and applications of QSAR/chemometrics in lead optimization.

7. I have published over 125 research papers and chapters. I have (co)-edited several books, including the following titles: "Chemometric Methods in Molecular Design", "Advanced Computer-Assisted Techniques in Lead Discovery", "Structure-Property Correlations in Drug Research", "Lipophilicity in Drug Action and Toxicology", "Computer-Assisted Lead Finding and Optimization", "Pharmacokinetic Optimization in Drug Research", "Pharmacokinetics and Metabolism in Drug Design", and "Drug Bioavailability".

8. I am secretary of the QSAR and Modelling Society, and I am on the editorial boards of several journals and the book series "Methods and Principles in Medicinal Chemistry". I have (co)-organised a number of symposia, e.g. in 1996 I was chairman of the 11th European Symposium on QSAR, held in Lausanne, Switzerland.

9. I have read and am familiar with US patent application no. 09/359,181 entitled "Computer-Aided Method for the Provision, Identification, and Description of Molecules Capable of Exhibiting a Desired Behavior, More Particularly in the Pharmaceutical Sector, and Molecules Obtained by Said Method" (hereinafter the '181 application). I have also reviewed the Office Action dated July 1, 2003 in the '181 application, in which the Examiner contends that the present specification is non-enabling with regard to the performance of dynamic filtering as called for in the claims. As a scientist having considerable knowledge, skill and experience in the field of the invention of the '181 application, I do not concur with the Examiner's contention.

10. Based on my consideration of the '181 application, it is my opinion that the definition and general overview of the characteristics and use of dynamic filters at page 9, line 3 to page 10, line 22 of the '181 application and the detailed description of the performance of dynamic filtering in relation to a specific example at page 35, line 3 to page 37, line 23 of the '181 application are sufficient to enable any person skilled in the art to make and use dynamic filters according to the invention.

11. The bases for my above-stated opinion are as follows:

a. Dynamic filtering is discussed in the aforementioned passages of the '181 application in terms of molecular dynamics (MD) analysis, autocorrelograms and principal component analysis (PCA).

b. MD and PCA are techniques, which are familiar to the skilled person. Indeed, to my knowledge software for performing MD simulations and PCA were publically available at the July 22, 1999 filing date of the '181 application.

c. Furthermore, from publications, such as the Eur. J. Med. Chem. reference mentioned at page 36 lines 4 and 5 of the '181 application, the skilled person would know how to generate autocorrelograms.

d. Thus the techniques for performing dynamic filtering are well known to researchers in the area.

e. The Examiner's enablement objection relies on an allegation that there is no description of how to use the Multidyn software referred to at page 17, lines 19 to 24 of the '181 application and no description of the parameters that make this software function. The objection appears to be based on a misconception that the '181 application Multidyn software is essential for the performance of dynamic filtering. In

fact, the skilled reader of the '181 application would understand from the passage at page 37, lines 16 to 18 that the Multidyn software is used to analyse trajectories and conformational spaces, i.e. it is merely an example of a convenient platform for applying PCA to autocorrelograms. As discussed at b. and c. above, the skilled person is not reliant on Multidyn to perform PCA and to generate autocorrelograms.

12. I further declare that all statements made herein of my knowledge are true, and that all statements made on information and belief, including those that can be supported by citations to published scientific literature, are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the '181 application or any patent issued thereon.

30 October 2003
DATE

HAN VAN DE WATERBEEMD, Ph.D.